REMARKS

Claims 12-14, 16, 19-23, 26-27 and 30-31 are currently pending and amendments to claims 12, 16, 19, 20, 23, 26, 27, 30 and 31 are submitted herewith. Support for the amendments may be found throughout the specification as originally filed, for example in the section entitled Brief Description of the Figures and Sequence Identifiers beginning at page 18, line 23; at page 24, line 18 through page 25, line 6; and at page 30, lines 14-15. No new matter has been added. The present amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Favorable reconsideration of the application is respectfully requested in view of the above amendments and the following remarks.

Claim Objections

Claims 12, 16, 20 and 27 stand objected to for the recitation of "wherein said at least one gene comprises a … (DPL1) gene **and** a … (LCB4) gene". The PTO asserts that this phrase does not make scientific or grammatical sense and suggests that the phrase should read "**or**" in place of "and".

Applicant respectfully disagrees and submits that the skilled artisan would readily understand that "at least one gene" means one, two, three, or more genes. Nonetheless, as presently amended, the claims no longer include the objected-to recitation, thereby obviating the objection. Withdrawal of the objection is therefore requested.

Claim Rejections – 35 U.S.C. § 112, first paragraph (written description)

Claims 12-14, 16, 19-23, 26-27 and 30-31 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description. In particular, the PTO asserts that the specification lacks description of representative species encompassed by the genus of DNAs used in the methods recited by the claims. As such, the PTO asserts that the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms

that a skilled artisan would recognize that Applicant was in possession of the claimed invention at the time of filing.

Applicant respectfully traverses these grounds for rejection. Without acquiescing to the rejection and solely to advance prosecution, Applicant has nevertheless amended claims 12, 16, 19, 20, 23, 26, 27, 30 and 31 to recite "wherein the nonendogenous SK comprises the amino acid sequence set forth in any one of SEQ ID NOs:19, 20, 21, 28 or 29, or a variant thereof having an amino acid sequence with at least 95% identity to the amino acid sequence of the nonendogenous SK, wherein the variant retains SK enzymatic activity…". Support for the present amendments can be found in the specification, for example, in the section entitled Brief Description of the Figures and Sequence Identifiers beginning at page 18, line 23; at page 24, line 18 through page 25, line 6; and at page 30, lines 14-15. These amendments are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Applicant respectfully submits that the specification as filed provides more than adequate written description for variants of the specifically recited SK polypeptides. Applicant also submits that as amended, the instant claims recite (i) a sufficient and relevant identifying structural characteristic shared by polypeptides of the recited genus, namely, their percentage of sequence identity to the sequences of the recited SK polypeptides, and (ii) a related sufficient and relevant functional characteristic, their SK enzyme activity. Applicant submits further that the skilled artisan would readily understand, in light of Applicant's disclosure, the single identifying characteristic common to the recited sequences, *i.e.*, SK activity of the polypeptides. Therefore, Applicant submits that the skilled artisan would recognize that Applicant was in possession of the claimed invention at the time the invention was filed. Reconsideration of the amended claims and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 112, first paragraph (enablement)

Claims 12-14, 16, 20-22, 26-27 and 30 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. In particular, the PTO concedes that the specification is enabling for a method of identifying an agent that modulates sphingolipid

metabolism using a mutant *Saccharomyces cervisiae* strain comprising a null allele of the endogenous DPL1 gene and/or LCB4 gene and/or YSR2 gene and transforming said mutant strain with a non-endogenous SK such as that encoding either SEQ ID NOs:19-21, 28 or 29, but asserts that the specification does not reasonably provide enablement for such a method using any mutant yeast strain comprising null alleles of any gene encoding any component of a sphingolipid pathway and expressing any non-endogenous gene of the sphingolipid pathway.

Applicant respectfully traverses these grounds for rejection. Without acquiescing to the rejection and solely to advance prosecution, Applicant has amended claims 12, 16, 19, 20, 23, 26, 27, 30 and 31 to recite "wherein the nonendogenous SK comprises the amino acid sequence set forth in any one of SEQ ID NOs:19, 20, 21, 28 or 29, or a variant thereof having an amino acid sequence with at least 95% identity to the amino acid sequence of the nonendogenous SK, wherein the variant retains SK enzymatic activity…". Support for the present amendment can be found in the specification, for example, in the section entitled Brief Description of the Figures and Sequence Identifiers beginning at page 18, line 23; at page 24, line 18 through page 25, line 6; and at page 30, lines 14-15. These amendments are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Applicant respectfully submits that the presently claimed methods are fully enabled by the specification as filed. In particular, Applicant submits that the instant specification more than adequately teaches a variety of techniques to determine % identity of a particular amino acid sequence relative to another, and to determine SK activity of a particular polypeptide (see, for example, specification at page 25, line 24-page 27, line 12 and page 49, line 3-page 50, line 17). Therefore, the skilled artisan would readily understand how to perform these assays in light of the instant disclosure. Applicant further submits that the skilled artisan would appreciate the routine nature of the techniques used in determining such activity, such that whether a particular candidate non-endogenous SK polypeptide has SK activity can be readily ascertained. Accordingly, Applicant submits that the instant claims are fully enabled by the specification as originally filed. Reconsideration of the amended claims and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 12-14, 16, 19-23, 26-27 and 30-31 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lanterman *et al.* (Biochem J. 1998 Jun 1; 332 (Pt 2):525-31), Kim *et al.* (Genetics 2000 Dec; 156(4):1519-29) and in view of Melendez *et al.* (Gene. 2000 Jun 13; 251(1):19-26 and GenBank Accession No. AF266756, created 6/1/2000). In particular, the PTO asserts in the Action that Lanterman *et al.* teach the creation of a yeast mutant strain comprising a null allele of the DPL1 gene, which strain is sensitive to sphingosine owing to its inability to degrade S-1-P. Lanterman *et al.* allegedly further teach that in double mutants where the LCB4 gene has also been knocked out, the mutant strain is no longer sensitive to sphingosine since the LCB4 kinase is no longer producing the S-1-P. The PTO concedes that Lanterman *et al.* do not teach a mutant yeast strain comprising a null allele of endogenous YSR2, and transforming such a mutant strain with non-endogenous SK. The PTO asserts that Kim *et al.* and Melendez *et al.* overcome this deficiency, while further conceding that neither Lanterman *et al.* nor Kim *et al.* teach methods of screening agents using a yeast system as presently claimed. The PTO relies on Melendez *et al.* as allegedly remedying this deficiency. As such, the PTO asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lanterman *et al.*, Kim *et al.*, and Melendez *et al.* to arrive at Applicant's invention.

As an initial matter, Applicant notes that the Action states at the bottom of page 8 that the application currently names joint inventors. Applicant submits that Julie D. Saba is the only inventor named on the application and is the sole inventor of the presently claimed invention.

Applicant respectfully traverses the rejection for the reasons already made of record and on the following grounds.

Applicant submits that the cited references, taken individually or for what they teach as a whole, do not teach or suggest an intact yeast phenotype rescue assay for screening inhibition of a non-endogenous SK. In fact, Lanterman *et al.* teach away from the present invention by disclosing that (D,L)-*threo*-dihydrosphingosine, a known inhibitor of mammalian SK, did not inhibit the yeast SK enzyme (see abstract, page 527, last paragraph and Figure 3),

suggesting that molecular pathway components of the yeast sphingolipid metabolism system have significant structural and functional differences from the mammalian sphingolipid metabolism system. As such, nowhere does the prior art suggest interchangeability between yeast and mammalian sphingolipid pathways of any constituent components, where if anything Lanterman *et al.* teach away from such use of heterologous SKs. Thus, the skilled artisan would not have had a reasonable expectation that a non-endogenous SK protein would function in a yeast system at all, let alone in the yeast phenotype rescue assay described by Applicant. As such, the skilled artisan would have had no motivation to combine the teachings of Lanterman *et al.* with the teachings of either Kim *et al.* or with Melendez *et al.*, nor could such an artisan reasonably have expected to do so successfully.

Even assuming, *arguendo*, that there would have been motivation to combine the teachings of Lanterman *et al.* with the teachings of Kim *et al.* and Melendez *et al.*, Applicant submits that the teachings of these secondary references do not overcome the deficiencies of Lanterman *et al.*, namely the lack of teaching therein, as admitted by the PTO at page 12 of the Action, of the presently disclosed mutant yeast strains expressing a non-endogenous SK protein as recited in the instant claims. In particular, as Applicant noted in the previous amendment filed December 1, 2006, Kim *et al.* merely describe the further characterization of the biological role of phosphorylated long chain bases in yeast. Kim *et al.* fail, however, to cure the deficiencies of Lanterman *et al.,* in particular by providing no actual teaching or suggestion with regard to the use of nonendogenous SK in a yeast screening assay.

Concerning Melendez *et al.*, the PTO asserts that this reference teaches an assay method to identify an inhibitor such as D,L-*threo*-dihydrosphingosine or N,N-dimethyl-sphingosine. Applicant disagrees with this assertion and submits that Melendez *et al.* merely confirm that the human SPHK1 protein that Melendez *et al.* have identified is indeed inhibited by these two well known sphingosine kinase inhibitors. This SPHK1 inhibition is shown, according to Melendez *et al.*, by simply exposing mammalian cell extracts to the inhibitors. No teaching or suggestion, however, is made by Melendez *et al.* of an assay involving intact yeast mutant strains, as would be required to practice the recited step of culturing a mutant yeast strain, nor do Melendez *et al.,* alone or in combination with any other documents, even remotely

contemplate screening other compounds for their ability to inhibit SPHK1, nor is a step of culturing yeast having nonendogenous SK in any way suggested.

Accordingly, Applicant submits that the primary and secondary references, taken individually or for what they teach as a whole, do not teach or suggest the claimed invention and in fact teach away from the present invention. Additionally, Applicant respectfully points out that the United States Supreme Court has recently noted that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (April 30, 2007, No. 04-1350; see also 82 U.S.P.Q.2d 1385; 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 WL 1237837), citing *United States v. Adams*, 383 U.S. 39. Therefore, Applicant submits that the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing. Reconsideration and withdrawal of the rejection are respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicant respectfully submits that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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